REMARKS

Reconsideration of the above-identified application in view of the amendments above and the remarks following is respectfully requested.

Claims 1-32 are in this case. Claims 1-11, 13-15, 17-18 and 20-32 have been withdrawn. Claims 12, 16 and 19 have been rejected. New claim 33 has now been added.

35 U.S.C. § 112, first paragraph Rejections

The Examiner has rejected claim 16 under 35 U.S.C. 112, first paragraph as failing to comply with the written description requirements.

The Examiner states that the specification is enabling for a method of extending a nascent oligonucleotide-3'-OH in a template dependent manner, comprising the step of contacting the nascent oligonucleotide with a nucleic acid template, a template dependent polymerase and 4^N oligonucleotide triphosphates each including N monomers, wherein N is an integer of 2 or 3. However, the Examiner asserts that the specification is not sufficiently enabling for a method employing an oligonucleotide of 4 or more monomers. The Examiner rejection is respectfully traversed. New claim 33 has been added.

The Examiner points out that there is no indication in the specification that an oligonucleotide triphosphate comprising four or more monomers is capable of being incorporated by template dependant polymerization. The Examiner asserts that undue experimentation is necessary for one of ordinary skill in the art because: (i) the Examples provide only a limited teaching wherein di- and tri-nucleotides are analyzed in a template-dependant polymerization assay; (ii) no information is provided in the specification that would enable one of ordinary skill in the art to make or use any oligonucleotide triphosphate comprising four or more monomers with any template dependant polymerase; (iii) no direction or guidance is provided in the specification that would enable one of ordinary skill in the art to incorporate or obtain oligonucleotide triphosphates comprising four or more monomers with any template dependant polymerase; (iv) incorporating oligonucleotide triphosphates comprising four or more monomers is not reproducible due to the lack of guidance presented in the specification; and (v) the level of unpredictability of incorporating

oligonucleotide triphosphate comprising four or more monomers in a nascent oligonucleotide is very high.

In support of unpredictability associated with incorporation of large oligonucleotide triphosphates in a nascent oligonucleotide, the Examiner cites Moroney *et al.* (Biochemistry 30: 10343 – 10349, 1991) stating that "the incorporation of dinucleotides and trinucleotides into the product represents the limit of tolerance for the polymerase, and longer oligonucleotides, although complementary to the template strand, cannot be incorporated as initiating nucleotides". In addition, the Examiner points out that in the extension assay described in Example 7 of the instant application, the incorporation of dinucleotides in extending a nascent oligonucleotide is at a higher efficiency than the incorporation of trinucleotides.

Applicant wishes to point out that while the efficiency of incorporating oligonucleotide triphosphates having 4 or more monomers by a specific polymerase enzyme may be lower than that of shorter oligonucleotide triphosphates (as was described in Example 7), lower efficiency does not necessarily indicate inoperability or inaccuracy of a reaction. For example, several recent DNA polymerase enzymes used in PCR are substantially less efficient (in terms of synthesis rate and template detection) than the original Taq polymerase, but are useful for their very high fidelity. Moreover, natural polymerases involving DNA synthesis and repair in vivo posses desirable characteristics in terms of their specificity and fidelity rather than synthesis rate (see, for example Napolitano *et al.*, EMBO J. 19:6259-65, 2000 and Boudsocq *et al.*, J Biol Chem. 279:32932-40, 2004).

In contrast to Examiner's assertion, the teachings of Moroney *et al.* do not provide any indication as to the operability of the present invention. Moroney *et al.* teach use of di- or trinucleotides forming abortive initiation products in RNA-synthesis. Although Moroney *et al.* teach that "...dinucleoside tetraphosphate can prime RNA synthesis but is ineffective as an elongation triphosphate" it should be noted that the present invention teaches the use of oligonucleotide triphosphates for primer extension during DNA synthesis, a process which radically differs from transcription initiation both chemically and dynamically. The priming of RNA-transcription requires recruitment of RNA-polymerase to a promoter region, and

then synthesis of dinucleotide primers, which can be extended by additional incoming mono-nucleotide triphosphates; in contrast, the DNA primer-extension of the present invention is achieved by linking between the 3'OH of the primer, and the triphosphate group at the 5' end of the incoming building block (that can be either 2 or 10 mer oligonucleotide), and thus, this type of synthesis should not be significantly influenced by the length of the added building block. Therefore, the operability of incorporating an oligonucleotide triphosphate comprising four or more monomers as an initiating primer during transcription (according to Moroney *et al.*) is entirely irrelevant to template dependent primer-extension using oligonucleotide triphosphates of 2 or more monomers.

Since the incorporation of oligonucleotides having 2 or 3 monomers onto a nascent oligonucleotide has already been successfully demonstrated using a single specific polymerase (Taq DNA polymerase; Example 7 of the instant application), it should be well within reason to anticipate that oligonucleotide triphosphates having four or more monomers may also be successfully incorporated to a nascent oligonucleotide using a similar, or another polymerase enzyme selected or generated capable incorporating the large oligonucleotide triphosphates according to the teaching of the instant application.

Applicant further wishes to point out that an ordinary person skilled in the art would have no difficulty synthesizing and purifying oligonucleotide triphosphates comprising four or more nucleotides using the procedure described in Examples 1 and 2 of the instant application. An oligonucleotide of four or more monomers can be readily ordered from numerous commercial providers of custom made synthetic oligonucleotides, or by synthesis using standard methods well known in the art. The oligonucleotide can then be converted to the triphosphates form as described in Example 1. The synthesized oligonucleotide triphosphates can be purified essentially as described in Example 2.

In addition, the instant application teaches using a variety of naturally-occurring polymerase enzymes (see, for example, on page 9 line 35 to page 10 line 16), as well as engineered polymerase enzymes <u>having increased activity and/or specificity in incorporating oligonucleotide triphosphates onto a nascent oligonucleotide in a template dependent manner</u> (see, for example, on page 14 line

32 to page 17 line 34). Thus, it should be well within the ability of an ordinary person skilled in the art to implement the teaching of the instant application in order to obtain, isolate or generate a polymerase enzyme capable of incorporating oligonucleotide triphosphates having 4 or more monomers onto a nascent oligonucleotide in a template dependent manner.

In view of the above arguments, Applicant believes that the specification of the instant application is sufficiently enabling to an ordinary person skilled in the art to make and use the method of the present invention having oligonucleotide triphosphates of 4 or more monomers as building blocks, without undue experimentation.

35 U.S.C. § 102 Rejections

The Examiner has rejected claim 12 under 35 U.S.C. § 102(b) as being anticipated by Moroney *et al.* (Biochemistry 30: 10343 – 10349, 1991). The Examiner's rejections are respectfully traversed.

The Examiner points out that Moroney *et al.* teaches incorporation of dinucleotide triphosphates during RNA transcription by a template-dependent polymerase in a template dependant manner. The Examiners asserts that Moroney *et al.* describes the method of claim 12 of the instant application.

Claim 12 of the instant application recites "A method of extending a nascent oligonucleotide-3'-OH in a template-dependent manner, the method comprising the step of contacting the nascent oligonucleotide-3'-OH with a nucleic acid template, a template-dependent polymerase and at least one oligonucleotide triphosphate under conditions in which said nascent oligonucleotide-3'-OH hybridizes with said nucleic acid template and said template-dependent polymerase is active in incorporating said at least one oligonucleotide triphosphate onto a growing 3'-OH group of the nascent oligonucleotide-3'-OH, thereby extending the nascent oligonucleotide-3'-OH in a template-dependent manner."

Moroney *et al.* describes the transcription of template (Tp6) encoding the pppGAUGGC transcript with an RNA polymerase (T7) in the presence of a radioactively-labeled dinucleotide triphosphates (either pppGpA or pppGpA) and the

nucleotides UTP, CTP and GTP. The reference describes the incorporation of the dinucleotide in the resulting transcript product as an initiating nucleotide (see Moroney *et al.* page 10347, col. 2, lines 4-10, 45-60).

Applicant wishes to point out that the teaching of the present application as recited in claim 12 is distinct and different from the teaching of Moroney *et al.* Thus, while the present invention teaches extending a nascent oligonucleotide with oligonucleotides, Moroney *et al.*, in sharp contrast, teaches initiating an RNA transcript with an oligonucleotide and extending the nascent oligonucleotide with nucleotide monomers.

Furthermore, it should be noted that Moroney *et al* in fact teaches away from the present invention. For example, in the last two lines of the Abstract, it is stated: "... a dinucleotide is not used as substrate for subsequent chain elongation in T7 RNA polymerase catalyzed transcription reaction."

Similarly, on page 10349, col. 1, third paragraph, lines 5-8 of Moroney *et al*, it is stated that: "With use of this template, it was established that the dinucleotide tetraphosphate **could not** serve as a substrate for incorporation by T7 RNA polymerase at an "internal" position in the nascent RNA chain."

Furtheremore, on page 10349, last forth (last) paragraph, lines 10-13 of Moroney *et al*, it is stated that: "The results presented here reinforce this notion in that dinucleoside tetraphosphate can prime RNA synthesis **but is ineffective as an elongation triphosphates**".

Hence, clearly, Moroney *et al.* does not anticipate or render obvious the invention as recited in claim 12 of the present application.

The Examiner has rejected claim 19 under 35 U.S.C. § 102(b) as being anticipated by Moroney *et al.* The Examiner's rejections are respectfully traversed.

The Examiner points out that Moroney *et al.* teaches incorporation of dinucleotide triphosphates during RNA transcription in a template dependant manner. The Examiners asserts that Moroney *et al.* describes the method of claim 19 of the instant application.

Claim 19 of the instant application recites "A method of extending a nascent oligonucleotide-3'-OH in a template-dependent manner, the method comprising the

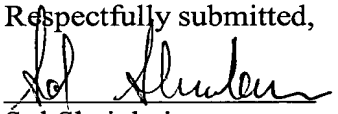
step of contacting the nascent oligonucleotide-3'-OH with a nucleic acid template, a template-dependent polymerase, at least one oligonucleotide triphosphate and at least one nucleotide triphosphate, wherein said at least one oligonucleotide triphosphate and said at least one nucleotide triphosphate are selected such that at least one monomer of said at least one oligonucleotide triphosphate is absent from said at least one nucleotide triphosphate, under conditions in which said nascent oligonucleotide-3'-OH hybridizes with said nucleic acid template and said template-dependent polymerase is active in incorporating said at least one oligonucleotide triphosphate and said at least one nucleotide triphosphate onto a growing 3'-OH of the nascent oligonucleotide-3'-OH, thereby extending the nascent oligonucleotide-3'-OH in a template-dependent manner."

As is argued hereinabove with respect to claim 12 rejections, Applicant is of the strong opinion that Moroney *et al* does not anticipate the present invention and in fact teaches away from it.

In view of the above arguments, Applicant believes to have overcome the 35 U.S.C. § 102 rejections.

Therefore it is respectfully submitted that claims 12, 16 and 19 are now in condition for allowance. Prompt Notice of Allowance is respectfully and earnestly solicited.

Respectfully submitted,



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